

Constant challenges and evolution of US military transfusion medicine and blood operations in combat

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BACKGROUND: Blood operations are constrained by many limitations in combat settings. As a result there are many challenges that require innovative solutions.

STUDY DESIGN AND METHODS: This is a descriptive overview of blood product usage and transfusion medicine adaptations that have been employed by the US military to support combat operations in Iraq and Afghanistan between November 2001 and December 2010.

RESULTS: Transfusion medicine challenges have included the need for rapid transport of large quantities of blood products from the United States to Iraq and Afghanistan, risks and appropriate countermeasures associated with blood products collected in the theater of operations, availability of fresh-frozen plasma at forward surgical facilities, need for platelets (PLTs) in combat, and the need to support constant and evolving changes in transfusion and resuscitation protocols. A decrease in the storage age of red blood cells (RBCs) transfused to combat casualties has been achieved. There has been an increase in the ratio of plasma and PLTs to RBCs transfused, increased availability of plasma and apheresis PLTs to facilitate this approach, and a continuous effort to improve the safety of using fresh whole blood and apheresis PLTs collected in combat. A number of clinical practice guidelines are in place to address these processes.

CONCLUSION: This multidisciplinary approach has successfully addressed many complicated and challenging issues regarding blood operations and transfusion practices for combat casualties.

Since the advent of blood typing and the development of anticoagulation solutions just before World War I (WWI), transfusion medicine has been an integral aspect of military combat operations. It has always been challenging for health care providers to optimally resuscitate patients with hemorrhagic injuries during combat due to the difficulties of providing safe and adequate blood supplies under austere conditions.

During WWI, whole blood was the primary resuscitation fluid.^{1,2} In WWII and the Korean War, lyophilized plasma, albumin, and whole blood were each transfused.^{1,2} The conflict in Vietnam saw the introduction of crystalloid infusions and component therapy in the form

ABBREVIATIONS: ASWBPL = Armed Services Whole Blood Processing Laboratory; CENTCOM = Central Command; MTF(s) = medical treatment facility (-ies); WWI (-II) = World War I (II).

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of red blood cells (RBCs), fresh-frozen plasma (FFP), or modified whole blood transfusion.¹ In all military campaigns of the past century fresh whole blood collected on site from fellow military personnel has been used to supplement all of the above methods of resuscitation for patients with hemorrhagic traumatic injuries.¹ The risk of transmission of infectious agents and hemolytic reactions associated with blood products collected in combat has always been a concern for military health care providers. Current clinical practice guidelines allow for the collection of fresh whole blood only when other blood products are unable to be delivered at an acceptable rate to sustain the resuscitation of an actively bleeding patient or when specific components such as RBCs, platelets (PLTs), cryoprecipitate, and FFP are not available.³ Due to the short shelf life of PLTs, apheresis PLTs are also collected at US military hospitals in Iraq and Afghanistan and distributed to surgical hospitals with high demand.

Recent literature describing increased risk to critically ill patients who receive RBCs of advanced storage age have also raised concern regarding the storage age of RBCs that are being transfused into combat casualties.^{4,5} US military logisticians, blood bankers, and clinicians have worked together to continually improve the process of collecting, shipping, and transfusing blood products at military treatment facilities during combat, as well as to improve the safety of the products made available to wounded soldiers. Our objective in this review is to demonstrate that a multidisciplinary approach to addressing transfusion practices and policies may improve outcomes for combat-related casualties and has significant potential to improve care in the future.

MATERIALS AND METHODS

The following is a description of the accomplishments of the military combat casualty care community at deployed military medical facilities during recent combat operations in Iraq and Afghanistan. Data presented have been obtained from different sources including the Armed Services Blood Program Office, the Joint Theater Trauma Registry, and Central Command (CENTCOM) and were collected between November 2001 and December 2010.

RESULTS

Transport system of blood products from military blood donor centers to military treatment facilities

A high degree of organization and coordination between US military services and the Armed Services Blood Program personnel is required to safely collect, manufacture, and ship hundreds of thousands of blood products from the United States to Iraq and Afghanistan to more than 50 medical treatment facilities (MTFs), many of which are in remote areas of both countries.

Blood supplies are collected, processed, and manufactured at Army, Navy, and Air Force blood donor centers throughout the United States and shipped to central shipping facilities in New Jersey and California for shipment overseas. This facility, known as an Armed Services Whole Blood Processing Laboratory (ASWBPL), is responsible for reconfirming the blood type of RBCs and for storing blood products at the correct temperatures while awaiting guidance on the number and blood types of RBCs and frozen blood products to ship. Whole blood is not actually separated into components at the ASWBPL. The name comes from the fact that when ASWBPL operations started in 1955, whole blood was the product of choice.

Once the CENTCOM request is received via secured channels, the ASWBPL palletizes boxes and delivers them for shipment on a weekly flight. After approximately 15 hours in the air with one refueling stop, the blood products arrive at an Air Force expeditionary blood transshipment system in the Middle East. From the expeditionary blood transshipment system, blood products are transported within hours to the blood support detachments in Iraq and Afghanistan. The blood support detachments in the theater coordinate the movement of blood products via air or ground to individual MTFs. To increase the efficiency of this process and to meet a request for fresher RBCs in combat, this entire process was revamped in November 2008. Changes were made to processes at all facilities and a second weekly flight was added. As a result, the age of blood arriving in the theater of operations has decreased a mean age of 7.2 days after collection in 2009 and 2010 (Fig. 1). Emphasis in the past 2 years has been on treating massively transfused (≥ 10 units of RBCs in 24 hr) casualties with RBCs less than 14 days old.

Volume and distribution of blood products transfused in the theater

Maintaining an adequate supply of all blood products that might be needed to resuscitate all incoming casualties at all MTFs is challenging under combat operations. Efforts are made to distribute the blood products that are expected to be utilized at each MTF while minimizing wastage. Since it is difficult to know when a mass casualty situation may take place, a conservative approach is frequently used to allocate blood supplies to medical facilities in the theater. A series of daily blood reports are generated by each facility to track utilization, current inventory, and future needs. Subsequent shipments are based on these daily blood reports. The Armed Services Blood Program Office is constantly in touch with operational planners to ensure that enough blood supplies are available wherever and whenever they are needed.

From November 2001 to December 2010, more than 258,000 units of blood products had been transfused to more than 26,000 US military personnel, local civilians,

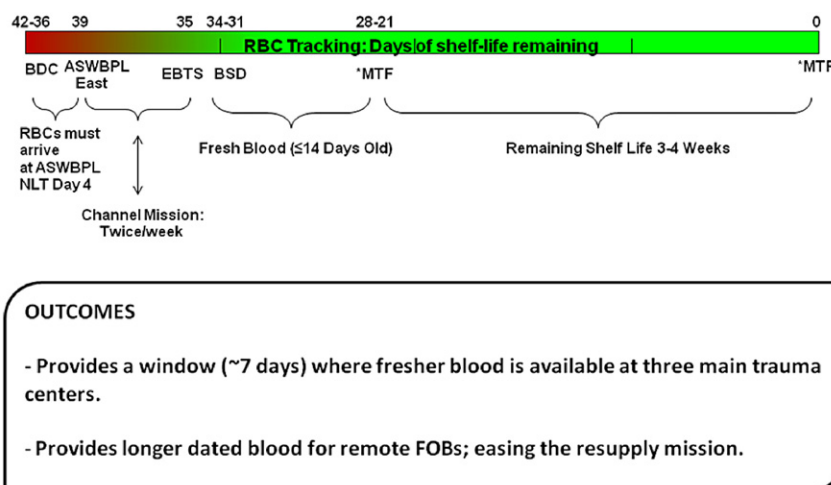
third-country nationals, and enemy combatant casualties in both Afghanistan and Iraq (Tables 1 and 2).⁶ Blood products are being transfused in high volumes: for example, one recent patient received 143 units of RBCs, another patient received 39 units of apheresis PLTs, and a third was given 258 units of FFP. In each case, these blood products were transfused to non-US military personnel (foreign nationals or non-US coalition forces). Previously published literature has also indicated that fresh whole blood collected on site from US military personnel is transfused in equal amounts and proportions, after adjusting for severity of injury, to foreign national and enemy combatants compared to US coalition patients.⁷ Table 2 indicates the distribution of blood products transfused to each of these populations. While transfusions peaked in Iraq in 2006 and have significantly decreased every year since, in Afghanistan transfusions in 2010 were almost seven times higher than in 2006 (Fig. 2).⁶

Change in ratio of blood products transfused to massive transfusion patients

Severe trauma casualties in both military and civilian settings have a high incidence of coagulopathy upon admis-

sion.^{8,9} Since the primary cause of preventable deaths for trauma patients is from hemorrhage^{10,11} and death from hemorrhage usually occurs within 12 hours of admission,^{12,13} an approach focusing on aggressively controlling coagulopathy early was applied to the casualties arriving at the 31st Combat Support Hospital in Baghdad during 2004.¹⁴ Performed in concert with damage control surgery, this approach has since been termed damage control resuscitation or hemostatic resuscitation.¹⁵⁻¹⁷ Adjusted results from retrospective analyses of large cohorts of massive transfusion patients indicate that transfusing increased ratios (>1:2) of plasma to RBCs and PLTs to RBCs are independently associated with improved survival and decreased death from hemorrhage.^{18,19} These results have been replicated in many civilian studies in both penetrating and blunt injury patients.¹⁷ The major limitation of these analyses is the potential for survivorship bias. Despite this concern, an emphasis was placed on the early use of plasma and PLTs for patients requiring massive transfusion for life-threatening hemorrhage from traumatic injuries. Today, the Joint Theater Trauma System clinical practice guideline for massive transfusion indicates that a 1:1:1 ratio of plasma, RBCs, and PLTs should be

transfused until bleeding can be controlled. This approach is recommended to treat the acute coagulopathy of trauma and prevent dilutional coagulopathy from developing. Increased availability of plasma and apheresis PLTs at all combat support hospitals in Iraq and Afghanistan has supported the application of this clinical practice guideline. Furthermore, the availability of plasma at forward surgical teams and other smaller and remote treatment facilities has allowed for increased and earlier use of plasma at these locations. As a result, the ratio of plasma to RBCs now approaches 1:1 at almost all military treatment facilities in Afghanistan where most of the massive transfusions have recently taken place (Fig. 3). Data from Afghanistan in massive transfusion patients, between October 2009



OUTCOMES

- Provides a window (~7 days) where fresher blood is available at three main trauma centers.
- Provides longer dated blood for remote FOBs; easing the resupply mission.

Fig. 1. Revamped timeline and intermodal distribution lanes of CENTCOM RBC shipments in the US to combat MTFs in Iraq and Afghanistan. BDC = blood donor center; BSD = blood support detachment; EBTs = expeditionary blood transshipment system; FOBs = forward operating bases; NLT = no later than.

TABLE 1. Total number of patients and units and mean number of units per patient transfused of each blood product from November 2001 to December 2010 (Operation Iraqi Freedom and Operation Enduring Freedom combined)

Blood product	Total number of patients	Total number of units	Mean number of units	Maximum number of units
Fresh whole blood	1,364	8,259	6.1	61*
RBCs	24,543	140,138	5.7	143*
Apheresis PLTs	3,311	7,772	2.3	39*
FFP	12,716	80,919	6.4	258*
Cryoprecipitate	2,123	21,670	10.2	114*

* Denotes transfused to non-US patient.

TABLE 2. Distribution of each blood product transfused to US and non-US casualties from November 2001 to December 2010 (Operation Iraqi Freedom and Operation Enduring Freedom combined)*

Units	US only	Non-US
Fresh whole blood	4,316 (52.3)	3,943 (47.7)
RBCs	38,478 (27.5)	101,660 (72.5)
Apheresis PLTs	2,929 (37.7)	4,843 (62.3)
FFP	24,237 (30.0)	56,682 (70.0)
Cryoprecipitate	8,316 (38.4)	13,354 (61.6)

* Data are reported as number (%).

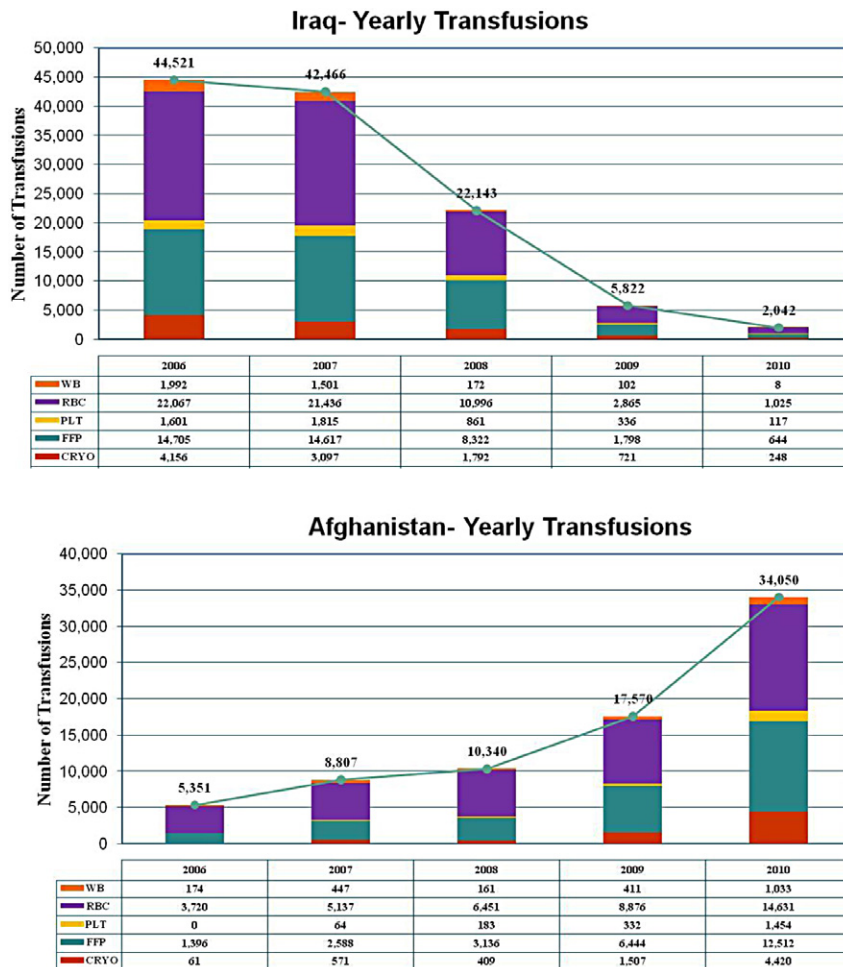


Fig. 2. Number of blood products transfused in Iraq and Afghanistan at US military treatment facilities from January 2006 to December 2010. CRYO = cryoprecipitate; WB = whole blood.

and September 2010, indicate that 30-day survival is approximately 90%.⁶ These outcomes are favorable compared to the 30-day survival of 59% reported for massive transfusion patients in a recent multicenter US civilian study.²⁰ A prospective randomized controlled trial com-

paring high and low plasma-to-RBC ratios in patients requiring massive transfusion has been funded and will begin soon.

Plateletpheresis program

Until November 2004, random-donor or apheresis PLT units had not been available for use in US military treatment facilities in combat. This was due to the short shelf life of 5 days for PLTs and the logistical constraints of transporting PLTs long distances. Since patients can rapidly develop the acute coagulopathy of trauma and die quickly as a result, the lack of PLT availability diminished the ability to resuscitate these patients. Fresh whole blood collected on site has historically been used to supply a source of PLTs but carries with it a risk of transmitting infectious disease and rarely transfusion-associated graft-versus-host disease.^{1,5,14} The first wartime platelet apheresis program was implemented at the 86th Combat Support Hospital in Baghdad in November 2004 as a result of the need to provide PLTs to patients requiring massive transfusion.²¹ Currently, four sites in either Iraq or Afghanistan are collecting PLTs for distribution to other combat support hospitals within their area. More than 14,000 units of apheresis PLTs have been collected and more than 7000 transfused to more than 3000 patients since 2004 (Table 1). Apheresis PLTs collected in combat are collected with standard equipment and processed according to AABB standards except for infectious disease testing according to Food and Drug Administration (FDA) guidelines. However, transmission countermeasures are in place to decrease the risk of infection. Among these countermeasures are mandatory human immunodeficiency virus (HIV) screening of all military personnel deploying to theater; hepatitis B vaccination; rapid testing the day of donation for HIV, hepatitis C virus (HCV), and hepatitis B virus (HBV); donor questionnaires; use of "pedigreed" donors who are fully tested within 90 days of donation with all FDA-required infectious disease blood donor assays before they are allowed to donate; and bacterial detection cultures taken 24 hours after collection and monitored for up to 7 days. In addition, samples are collected from all donors the day of

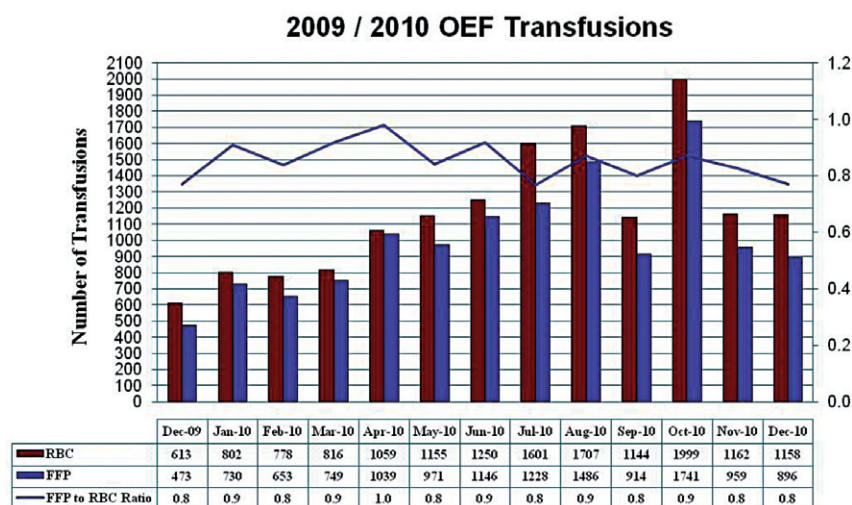


Fig. 3. Mean RBC and FFP use per month at US military treatment facilities during Operation Enduring Freedom (OEF) in Afghanistan from December 2009 to December 2010.

donation and tested retrospectively in the United States for all FDA-required markers. The ability to safely collect, store, and transfuse apheresis PLTs at a combat support hospital has never been achieved before and is a significant advancement of combat medicine.

Fresh whole blood transfusion program

Fresh whole blood has been an option for transfusion to casualties during combat since WWI due to its immediate availability from the “walking blood bank” and its effectiveness. Fractionation techniques and storage solutions developed after WWII improved the utilization and increased the storage time of blood products. Consequently, the need for whole blood transfusions has decreased but continues to be an effective alternative in austere combat settings.

In the early stages of the Iraq war, fresh whole blood was typically transfused during the late stages of the resuscitation as a salvage effort in the setting of an established coagulopathy. Fresh whole blood in these circumstances was used primarily as a source of PLTs since RBCs and plasma were almost always routinely available at combat support hospitals. Forward surgical teams and other far-forward facilities typically had only RBCs available for transfusion. Physicians at these locations would transfuse whole blood as a source of plasma and PLTs typically only after severe coagulopathy developed. In 2004, the combat support hospital in Baghdad made many efforts to increase the efficiency of the use of fresh whole blood for patients with life-threatening injuries.^{7,14} In an attempt to decrease the risk of certain transfusion-transmitted diseases, the use of non-FDA-approved rapid tests were employed for the first time at a US military combat hospi-

tal.^{7,14} To avoid the development of anemia in whole blood donors (who were primarily the hospital staff), a system of recruiting volunteers from US military personnel within the green zone in Baghdad was developed. Rosters of volunteers according to blood type were developed and maintained by local medical leadership. Additionally, volunteer donors were prescreened by questionnaire to determine eligibility. This significantly increased the potential donor pool and the rate at which donors could be screened for eligibility. Ultimately, the speed of collection and transfusion of fresh whole blood increased.^{7,14} Due to the large number of severely injured patients at the combat support hospital in Baghdad in 2004, experience with fresh whole blood increased quickly. Favorable clinical

outcomes anecdotally attributed to whole blood reversal of shock and coagulopathy encouraged earlier use of fresh whole blood in the resuscitation of patients with life-threatening injuries.^{7,14} In September 2004, a massive transfusion guideline was developed that incorporated the early use of fresh whole blood.¹⁴ The system as described above has been standardized and is now used for screening and identification of blood donors throughout the theater of operations and is the topic of a recently published clinical practice guideline.³

The use of fresh whole blood is not controversial in the resource-limited setting where plasma or PLTs are not available for a casualty with severe hemorrhagic shock. Controversy still remains, however, regarding criteria for use of fresh whole blood when all other blood components are available.^{4,22} A number of investigators and clinicians have reported anecdotal experiences related to positive outcomes in these settings (see below), and it is plausible that factors available in a freshly collected unit of blood are lost during the separation and storage process. However, the current clinical practice guideline allows for the collection and transfusion of fresh whole blood only when specific blood components are not available or are unable to be delivered at an acceptable rate to sustain the resuscitation of an actively bleeding patient or when stored components are not adequately resuscitating a patient with an immediately life-threatening injury.³ The availability of RBCs and plasma in most MTFs and PLTs at US military combat support hospitals has played a role in the marked decrease in the number of fresh whole blood units collected in the theater.

Whether fresh whole blood is more advantageous in this patient population is currently unknown due to the many confounding variables in retrospective studies and

lack of any prospective studies. Two recent reports suggest that the partial use of fresh whole blood (20%-30% of blood volume transfused) compared to 100% use of stored components is associated with improved 24-hour survival with conflicting results for 30-day survival.^{23,24} A prospective randomized controlled study is under way in Houston to determine if whole blood has any advantages over component therapy in patients with traumatic injuries in hemorrhagic shock.

Infectious disease testing of fresh whole blood and PLTs

Technology, time, and regulatory constraints preclude implementation of standard FDA-mandated infectious disease screening in support of current combat operations. To mitigate this risk, US CENTCOM guidance is to perform rapid testing of all emergency fresh whole blood and apheresis PLT donors before transfusion. Rapid assays are available in the theater to the level of forward surgical facilities for HIV-1/2 antibody, HBV surface antigen, and HCV antibody. Additionally, research examining the potential use of pathogen reduction technologies for whole blood and PLTs are being performed.

The urgent need to identify means to rapidly test blood collected in theater during the initial stages of the war (2004-2006) led medical personnel to acquire rapid tests for hepatitis B and C that ultimately proved to be insensitive. In 2007, with the use of serum panels from recently infected individuals, the BioRapid HBsAg and HCV rapid tests were both determined to have specificity of 100%, but very low sensitivities of 15 and 28%, respectively. As a result of these findings the US Department of Defense published a request for the development of accurate rapid screening tests for HBV and HCV. By 2008, superior rapid assays for both HBsAg and HCV with specificities of 100% and sensitivities of 85 and 95%, respectively, had been independently analyzed by the US military and deployed to all facilities collecting blood in theater. A rapid test for HIV-1/2, which is FDA-approved for diagnostic use (but not for screening of blood products), has been used in theater for several years. More recently, an FDA-approved for diagnostic use HCV rapid test with a 99% specificity and sensitivity was deployed. In addition, there are current efforts toward the development of a multiplexed rapid diagnostic platform for HIV, HBV, and HCV. Forward thinking on the part of Armed Services Blood Program Office and United States Army Center for Health Promotion and Preventative Medicine led to an epidemiologic consultation to specifically characterize transfusion-transmitted infection epidemiology associated with emergently collected blood product transfusion.²⁵ This study carefully investigated 761 recipients of emergently collected blood products for incident HCV, HIV, and HBV infection. Of the approximately 470 recipi-

ents who underwent posttransfusion testing, no HIV nor HBV incident infections were identified. One HCV transmission was identified (rate 2.1/1000 persons) in this study. By solely evaluating US military personnel who were deployed in support of Operation Iraqi Freedom or Operation Enduring Freedom, transfusion-transmitted infection prevalence among potential walking blood bank donors was estimated at 8 in 1000 and 4 in 1000 for HCV and chronic HBV, respectively. These results demonstrate that although the transfusion-transmitted infection risks are low, a nonzero risk exists that underscores the need for both risk-benefit analysis before using emergently collected blood products as well as the need for countermeasure development and deployment.

Storage age of RBCs

According to data collected by the Armed Services Blood Program Office in April 2008, the mean age of units on the shelf at all combat support hospitals was 32 days. As a result of retrospective studies indicating increased risk of morbidity and mortality with the use of RBCs stored for more than 14 days, and the fact that the mean and mode age of RBCs transfused to massive transfusion casualties in Iraq was determined to be 33 and 42 days, respectively,⁵ efforts were initiated in late 2008 to expedite the delivery of these RBCs to the theater.

The current massive transfusion clinical practice guideline preferentially calls for transfusing RBCs of not more than 14 days of storage time to these patients.³ As a result, the mean storage age of RBCs transfused to these patients has decreased to a mean (\pm standard deviation) of 23 (\pm 11.2) days. Randomized controlled clinical trials are under way to determine if the use of RBCs of decreased storage age can improve outcomes. The Department of Defense is taking an active role in supporting these trials.²⁶

Frozen blood products

Given the logistic issues related to transporting blood products to widely distributed medical facilities throughout the theater of operations, the use of frozen cellular blood components such as RBCs and PLTs has been explored. Use of these products allows long-term storage with appropriate screening and was initially described for combat situations in 1967.²⁷ Both frozen RBCs (United States) and PLTs (the Netherlands) are currently being utilized by coalition forces in areas of combat operations.²⁸

The first operational blood bank utilizing frozen RBCs was established in 1956 at Chelsea Naval Hospital (Boston, MA), in part to evaluate the feasibility of frozen blood usage aboard Navy ships. In 1966 the first frozen blood bank in a combat zone was established at Navy Station Hospital, DaNang, Republic of South Vietnam. Over a 7-month period, 465 previously frozen RBC units were

transfused to severely injured casualties, both as the primary RBC product and in combination with liquid RBCs.²⁷ In 1985 an additional 68,000 RBC units were frozen by the US Department of Defense and were positioned in several areas around the globe to support current and future military medical expeditionary or contingency operations.

Frozen and deglycerolized RBCs are initially derived from 450 mL of whole blood collected in CPDA-1 collection bags. The RBCs are stored for 3 to 6 days at 1 to 6°C before being frozen in a cryoprotectant (40% m/v glycerol) and stored in the frozen state at -65°C or colder. FDA-approved frozen and deglycerolized RBCs are currently being used at combat support hospitals in both Iraq and Afghanistan. Use of these units requires thawing (approx. 45 min) and then removal of the cryoprotectant by serial washing before suspension in preservative solution, which takes an additional 55 minutes. After deglycerolization, they are resuspended with AS-3 and stored at 1 to 6°C, until ready for transfusion. Frozen RBCs are FDA approved for transfusion for up to 14 days after deglycerolization.

The current indication in Afghanistan and Iraq for use of frozen and deglycerolized RBCs is as a supplement to liquid RBCs during surge periods of increased transfusion requirements to decrease casualty hemorrhagic morbidity and mortality. Experience with frozen RBCs is increasing and preliminary reports demonstrate no reports of severe adverse events and increases in hemoglobin and hematocrit similar to those associated with RBCs (D. Zierold, verbal communication, 2011).

The Netherlands military currently deploys a self-sufficient military blood bank facility in support of its military operations. This facility, consisting of frozen RBCs, plasma, and PLTs, has been deployed to Afghanistan and Iraq since 2004.²⁸ PLTs frozen with 4% DMSO can be safely stored at -80°C for 2 years and retain 50% of their aggregation properties.²⁹ Washing is not currently necessary, and the current protocol includes reconstitution with 1 unit of thawed plasma. The Netherlands military blood bank uses O PLTs with AB plasma, allowing transfusion into all blood types. Current published experience with cryopreserved PLTs is limited.^{28,30}

CONCLUSIONS

Despite the challenges of war in two theaters of operation, a number of improvements and changes to blood distribution and use policy have been developed over the past 10 years. The nature of medical care in combat operations is dynamic and constantly evolving. Combat casualty data are continuously evaluated as well as the level of evidence available to support policy in the theater. Before policy changes are made, the evidence is objectively weighed and outcomes are carefully monitored. Policies are sup-

ported by expert consensus and retrospective data. Prospective data to guide therapy are rarely available, since prospective, randomized clinical trials are almost impossible to complete in these combat environments and may require large numbers of patients to reach significant results. As a result, a number of clinical practice guidelines have been developed and are in broad use.³ The multidisciplinary approach of the US and coalition military medical community has successfully addressed many complicated and challenging issues regarding transfusion practices involving hundreds of thousands of blood products for thousands of patients. Collaborative efforts will continue to address transfusion medicine and other medical challenges that arise when striving to provide the highest quality and safest care to all patients injured during combat operations.

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We dedicate this review to the men and women of the US military who serve their country with honor, discipline, and courage. We especially dedicate this review to the servicemen and women who have paid the ultimate sacrifice and to their families.

CONFLICT OF INTEREST

PS is a consultant for CaridianBCT, Entegriion, and the US Army Institute of Surgical Research. No other conflicts for all other authors.

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